UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,229	04/27/2006	John William Chapman	056159-5261	6003

9629 7590 06/18/2008

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	
MAIL DATE	DELIVERY MODE
06/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,229	CHAPMAN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008 and 22 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-9 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-9 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1, 6-9, and 12-18 are pending in the application.

[2] Applicant's amendments to the claims, filed on 4/21/08 and 5/22/08, are acknowledged. The claim listing filed on 5/22/08 replaces all prior versions and listings of the claims. Claims 1, 6-8, and 13 have been amended; claims 2-5 and 10-11 have been canceled; and claims 14-18 have been added relative the claim listing filed on 6/16/05.

[3] Applicant's arguments filed on 4/21/08 in response to the Office action mailed on 1/22/08 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim to Priority

[5] As noted in a prior Office action, this application is a 371 filing of PCT/EP03/12219, filed on 11/3/03 and claims foreign priority under 35 USC § 119(a)-(d) to EPO 02258921.2, filed on 12/20/02. A certified copy of the foreign priority document was filed in the instant application on 6/16/05.

Claim Objections

[6] Applicant is advised that should claim 9 be found allowable, claim 13 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

[7] Claims 1, 14-15, and 17 are objected to in the recitation of "at least [ ]% homology" and in order to substantially improve claim form, it is suggested that the noted phrase be amended to recite, for example, "at least [ ]% amino acid sequence homology".

Claim Rejections - 35 USC § 112, Second Paragraph

[8] The rejection of claims 1-8 and 12 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "a type III antifreeze protein" is withdrawn in view of the amendment to claim 1 to limit the type III AFP to having "at least 80% homology to SEQ ID NO:1". In view of this amendment, a skilled artisan would recognize the scope of proteins that are considered to be type III AFP polypeptides.

[9] Claims 1, 6-9, and 12-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.

[a] Claim 1 (claims 8-9, 13-16, and 18 dependent therefrom) recites the phrase "deficient in protein mannosyl transferase...", which is a relative term that renders the claim indefinite. The term "deficient in protein mannosyl transferase..." is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that, for example, the claim define and clearly state as to what the level of pmt1 and/or pmt2 is being compared such that a skilled artisan could make a determination of whether or not the level is considered to be "deficient".

[b] Claim 17 is confusing in the recitation of "the yeast is a protein mannosyl transferase..." as yeasts are recognized in the art as being microorganisms and not proteins. It is suggested that applicant clarify the meaning of the noted phrase.

[c] Claim 17 is indefinite in the recitation of "functional equivalents thereof" because it is unclear as to what "function" is being referenced. It is acknowledged the specification defines "functional equivalent" as meaning "any polypeptide whose sequence has at least 80%, more preferably at least 85%, 90% or 95% sequence identity with the sequence of type III HPLC-12 as shown in SEQ ID NO: 1 and which exhibits AFP activity, in particular ice recrystallisation inhibitory (RI) activity" (p. 9, lines 10-14). However, it is unclear from this definition as to what function is intended as being "AFP activity", particularly as the disclosure of "in particular ice recrystallisation inhibitory (RI) activity" is an exemplary activity. For example, does the "function" refer to one that is specific or, to one that is generally applicable to any protein, *e.g.,* the ability

to elicit antibodies? It is suggested that applicant clarify the meaning of the noted phrase.

[d] Claim 17 is indefinite in the recitation of "a type III HPLC-12 antifreeze protein (AFP) and functional equivalents thereof...comprises expressing in a yeast host cell which is deficient in protein glycosylation, a nucleic acid sequence encoding the AFP" as it is unclear as to the scope of proteins that are produced by the claimed method. Because the active method step of the claim recites the use of "a nucleic acid sequence encoding the AFP", which is a narrow range limitation, but the preamble recites the broader range limitation "(AFP) and functional equivalents thereof", the claim is considered indefinite. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claim Rejections - 35 USC § 112, First Paragraph

[10] The written description rejection of claims 1, 6-9, and 12-13 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 8 beginning at p. 5 of the Office action filed on 1/22/08. Newly added claims 14-18 are included in the instant rejection for reasons that follow. Thus, claims 1, 6-9, and 12-18 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 5 of the 4/21/08 remarks, applicant argues the genus of type III AFP proteins produced by the claimed methods is adequately described by reciting "that the type III AFP have at least 80% identity to SEQ ID NO:1".

To the extent the rejection is based on the genus of type III AFP polypeptides, the rejection is withdrawn for reasons set forth below. While it is acknowledged that claim 1 recites "type III antifreeze protein" line 1 and claim 17 recites "type III HPLC-12 antifreeze protein" in lines 1-2, these limitations have not been interpreted as functional limitations of the genus of recited type III AFP proteins. Put another way, in the absence of a specifically recited functional limitation in the claims, the genus of type III AFP polypeptides has been interpreted as being functionally unlimited.

The recited genus of type III AFPs encompasses polypeptides comprising SEQ ID NO:1, as well as variants having 80%, 90%, and 95% homology to SEQ ID NO:1. However, the specification discloses only a single species of type III AFP polypeptides, *i.e.*, SEQ ID NO: 1. There are no other drawings or structural formulas disclosed or

sequences that have 80%, 90%, or 95% homology to SEQ ID NO:1. The recitation of a polypeptide with at least 80% homology represents a partial structure, that is, at least 80% percent of the amino acids in the polypeptide will match those in SEQ ID NO:1, and up to 20% of them may vary from those in SEQ ID NO:1. However, there is no teaching regarding which 20% of the amino acids may vary from SEQ ID NO:1. Consequently, there is also no information given about which amino acids will vary from SEQ ID NO:1 in the recited genus of type III AFP polypeptides. There is no functional limitation on the genus of recited proteins or any polypeptide having at least 80% structural homology to SEQ ID NO:1. The disclosure of SEQ ID NO:1 combined with the pre-existing knowledge in the art would have put one in possession of the genus of type III AFP polypeptides. With the aid of a computer, one of skill in the art could have identified all of the polypeptides with at least 80% amino acid sequence homology with SEQ ID NO:1. Thus, one of ordinary skill in the art would conclude that the applicant was in possession of the claimed genus at the time the application was filed.

Applicant further argues the genus of recited host cells used in the claimed methods has been limited to a yeast cell that is deficient in pmt1 and/or pmt2. According to applicant, the single disclosed representative species of *S. cerevisiae* having a deletion of pmt1 or pmt2 is sufficient to describe all members of the genus, particularly as the specification discloses identification of *K. lactis* homologues of *S. cerevisiae* pmt and pmt proteins are evolutionarily conserved.

Applicant's argument is not found persuasive. In this case, the claimed methods recite "the fungal host cell is deficient in protein mannosyl transferase 1 (pmt1) and/or

protein mannosyl transferase 2 (pmt2)", wherein the mechanism by which the yeast is "deficient" in pmt1 and/or pmt2 is unlimited and thus encompasses widely variant species of yeast host cells. Moreover, while the yeast of the methods of claims 1 and 17 is recited as being pmt1 and/or pmt2-deficient, there is no limitation by which the yeast is deficient in protein glycosylation, *i.e.,* the mechanism by which the yeast is protein glycosylation deficient is not limited to pmt1 and/or pmt2-deficiency. In this case, the examiner maintains that the single disclosed species of fungal host cells deficient in pmt1 and/or pmt2, *i.e.,* a *Saccharomyces cerevisiae* having a deletion of the pmt1 and/or pmt2 genes, fails to describe all members of the recited genus of yeast host cells. As noted in the prior Office action, while MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case, the recited genus of fungal cells encompasses widely variant cells, having any alteration that results in the fungal host being deficient in pmt1 and/or pmt2. Given the lack of description of a representative number of yeast cells that are "deficient" in pmt1 and/or pmt2, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[11] The scope of enablement rejection of claims 1, 6-9, and 12-13 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set

forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 9 beginning at p. 8 of the Office action filed on 1/22/08. Newly added claims 14-18 are included in the instant rejection for reasons that follow. Thus, claims 1, 6-9, and 12-18 are rejected herein.

RESPONSE TO ARGUMENT: At p. 6 of the 4/21/08 remarks, applicant argues the scope of type III AFP proteins produced by the claimed methods is fully enabled by reciting "that the type III AFP have at least 80% identity to SEQ ID NO:1".

Applicant's argument is not found persuasive. As noted above, while it is acknowledged that claim 1 recites "type III antifreeze protein" line 1 and claim 17 recites "type III HPLC-12 antifreeze protein" in lines 1-2, these limitations have not been interpreted as functional limitations of the recited type III AFP proteins. Put another way, in the absence of a specifically recited functional limitation, *e.g.*, ice recrystallization inhibitory activity, in the claims, the scope of type III AFP polypeptides has been interpreted as being functionally unlimited. In this case, the scope of polypeptides, being functionally unlimited, encompasses methods for producing SEQ ID NO:1 variant polypeptides that are, *e.g.*, non-functional and/or have an activity or activities other than that of SEQ ID NO:1 herein. The specification fails to provide guidance for using those polypeptides having activity other than ice recrystallization inhibitory activity. As such, the examiner maintains the position that the specification fails to enable the full scope of claimed methods. Moreover, it appears that the prior art recognizes the unpredictability in achieving antifreeze activity of any recombinantly produced type III AFP in a fungal host. As noted in the prior Office action, according to Chapman et al. (WO 97/02343;

cited in the IDS filed on 6/16/05), all fungally produced isoforms of Ocean Pout type III AFP with the exception of HPLC-12 failed to show "significant antifreeze activity" (p. 33, bottom). As such, it is highly unpredictable as to whether or not any fungally-produced type III AFP will exhibit antifreeze activity.

Applicant further argues the recited host cells used in the claimed methods has been limited to a yeast cell that is deficient in pmt1 and/or pmt2. According to applicant, the disclosure of an *S. cerevisiae* having a deletion of pmt1 or pmt2 is sufficient to enable all yeast host cells that are "deficient" in pmt1 and/or pmt2, particularly as the specification discloses identification of *K. lactis* homologues of *S. cerevisiae* pmt and pmt proteins are evolutionarily conserved.

Applicant's argument is not found persuasive. In this case, the claimed methods recite "the fungal host cell is deficient in protein mannosyl transferase 1 (pmt1) and/or protein mannosyl transferase 2 (pmt2)", wherein the mechanism by which the yeast is "deficient" in pmt1 and/or pmt2 is unlimited and thus encompasses any yeast host cell that is "deficient" in pmt1 and/or pmt2 by any modification. Moreover, while the yeast of the methods of claims 1 and 17 is recited as being pmt1 and/or pmt2-deficient, there is no limitation by which the yeast is deficient in protein glycosylation, *i.e.*, the mechanism by which the yeast is protein glycosylation deficient is not limited to pmt1 and/or pmt2-deficiency. In this case, the examiner maintains that the single disclosed working example of fungal host cells deficient in pmt1 and/or pmt2, *i.e.*, a *S. cerevisiae* having a deletion of the pmt1 and/or pmt2 genes, fails to enable all yeast host cells having any modification such that the resulting cell is "deficient" in pmt1 and/or pmt2 as

encompassed by the claimed methods. In this case, the specification and prior art fail to provide guidance regarding any other modification that results in a pmt1 and/or pmt2 deficient yeast strain.

As noted in the prior Office action, while MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case, the recited genus of fungal cells encompasses widely variant cells, having any alteration that results in the fungal host being deficient in pmt1 and/or pmt2. Given the lack of description of a representative number of yeast cells that are "deficient" in pmt1 and/or pmt2, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological

characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

[12] The rejection of claims 1, 6-9, and 12-13 under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. (WO 97/02343; cited in the IDS filed on 6/16/05; "Chapman") in view of Ng et al. (US Patent Application Publication 2002/0068325; "Ng") and Gentzsch et al. (*FEBS Lett.* 377:128-130, 1995; "Gentzsch") is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 10 beginning at p. 13 of the Office action filed on 1/22/08. Newly added claims 14-18 are included in the instant rejection for reasons that follow. Thus, claims 1, 6-9, and 12-18 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 6 of the 4/21/08 remarks, applicant argues:

> It is respectfully submitted that Ng discloses pmt mutants as a means to affect protein folding, not as a means to affect protein activity. As the specification states, it was thought in the art that glycosylation of AFPs was required for proteins to function *(see* specification at page 4, lines 7-23). Furthermore, the AFP as disclosed by Chapman is not produced in a glycosylation deficient cell, but yet is a functional protein with high antifreeze activity. Chapman, at page 4, lines 21-37, specifically states that the AFP produced "does not exhibit reduced activity." Accordingly, there was no motivation in the art at the time the present invention was filed to produce an unglycosylated AFP or even suggestion that unglycosylated AFP would be expected to function with any reasonable expectation of success. In fact, no reference indicates a suggestion that glycosylation may in fact reduce the activity of AFP.

> Furthermore, no cited reference demonstrates that the pmt1 and pmt2 enzymes glycosylate the AFP of the claimed invention. The Examiner acknowledged that there are six non-redundant pmt proteins in yeast with different substrate specificity. Accordingly, there is no guidance in the art as to which pmt glycosylates the AFP of the claimed invention.

Applicant's argument is not found persuasive. Applicant appears to take the position that one of ordinary skill in the art would not have used a pmt1- and/or pmt2-deletion strain of *S. cerevisiae* because it was thought that glycosylation of AFPs was required for antifreeze function. However, the specification at p. 4 would appear to suggest otherwise, stating (lines 22-23), "there is no clear indication of a general link between glycosylation and activity among AFPs".

Moreover, addressing applicant's argument that the specification's disclosed advantage relates to protein activity, not protein folding and that the prior art is silent with respect to glycosylation reducing the activity of AFP, it is noted that according to MPEP 2144.IV, "It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)". In this case, Ng discloses advantages for using a pmt1 or pmt2-deletion strain of *S. cerevisiae* for recombinant protein production, which is undisputed by applicant. In view of the disclosed advantages of using a pmt1 or a pmt2-deletion strain of *S. cerevisiae* for recombinant protein production as taught by Ng, one of ordinary skill in the art would have been motivated to combine the teachings of Chapman, Ng, and Gentzsch to modify the method of Chapman to use a pmt1- and/or a pmt2-deficient strain of *S. cerevisiae*.

Furthermore, in response to applicant's argument that the prior art is silent as to whether or not a Pmt polypeptide glycosylates HPLC-12 of SEQ ID NO:1 as taught by Chapman, regardless of whether or not the prior art provides such a teaching, Ng teaches that "it is possible that most heterologous proteins [produced in yeast] can become O-linked glycosylated" and that O-linked glycosylation can result in misfolding and compromise activity and stability (p. 6, paragraph 69). Because Ng teaches that possibly most heterologous proteins are O-linked glycosylated in yeast, and that using a pmt1- or pmt2-deletion strain of *S. cerevisiae* for recombinant protein production can reduce protein misfolding and enhance protein activity and stability, one of ordinary skill in the art would have been motivated to combine the teachings of Chapman, Ng, and Gentzsch to modify the method of Chapman to use a pmt1- and/or a pmt2-deficient strain of *S. cerevisiae*.

In order to clarify the record, it is noted that SEQ ID NO:1 herein, which is referred to as type III HPLC-12 (see sequence listing paper copy filed on 6/16/05), would appear to the same amino acid sequence as the type III HPLC-12 polypeptide as disclosed by Chapman (see, *e.g.,* Figure 1).

Claim Rejections – Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[13] Claims 1, 6-9, and 12-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of US Patent 7,297,516 ("'516 patent") in view of Ng (*supra*) and Gentzsch (*supra*). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The difference between claims 1, 6-9, and 12-18 and the claims of the '516 patent is that method of the claims of the '516 patent do not require the use of a pmt1 and/or pmt2-deficient yeast for protein production.

However, motivation to use a pmt1 and/or pmt2-deficient yeast for protein production is provided by the reference of Ng (*supra*). Ng teaches "In yeast, O-linked glycosylation begins in the ER through the action of a family of genes called protein mannosyltransferases (PMT)" (paragraph 68 at p. 6); teaches pmt1 and pmt2 mutant *S.*

cerevisiae strains, with inactivated pmt1 and pmt2 genes, respectively (paragraph 57 at p. 4); and teaches "These data show that heterologous proteins expressed in yeast are inappropriately modified by O-linked glycosylation. In turn, the modification can have negative consequences on the maturation and activity of the protein. The inventors have established that coupling expression using an endogenous signal sequence with specific mutant strains deficient in O-linked glycosylation, the activity of heterologous proteins expressed in yeast can be drastically improved. Since there are 6 PMT genes in yeast that are non-redundant and exhibit differences in substrate specificity, deletion strains of any of the six genes may provide the needed inhibition of aberrant O-glycosylation. In addition, mutations can be combined to further promote proper folding. Thus the inventors have developed a novel solution for overcoming a problem that has limited the potential of low cost expression of commercially important molecules in yeast" (paragraph 71 at p. 6).

Gentzsch teaches pmt1 and pmt2 deletion mutants of *S. cerevisiae* (p. 28, column 2, paragraph 2.1); teaches the polypeptides encoded by pmt1 and pmt2 function as a heterodimer having O-mannosyltransferase activity in the O-glycosylation of polypeptides (p. 128, abstract); and teaches that disruption of each of these genes leads to "a dramatic decrease of mannosyltransferase activity in vitro" (p. 128, abstract).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of the '516 patent to use a pmt1- and/or a pmt2-deficient strain of *S. cerevisiae*. One would have been motivated to do this because of the advantages of using such a strain as noted by Ng above.

[14] Claims 1, 6-9, and 12-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 6-11, and 14-17 of co-pending US Patent Application 10/450,211 ("'211 application") in view of Ng (*supra*) and Gentzsch (*supra*). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The difference between claims 1, 6-9, and 12-18 and the claims of the '211 application is that method of the claims of the '211 application do not require the use of a pmt1 and/or pmt2-deficient yeast for protein production and the heterologous protein is not limited to type III HPLC-12.

However, motivation to use a pmt1 and/or pmt2-deficient yeast for protein production is provided by the reference of Ng, which teaches "In yeast, O-linked glycosylation begins in the ER through the action of a family of genes called protein mannosyltransferases (PMT)" (paragraph 68 at p. 6); teaches pmt1 and pmt2 mutant *S. cerevisiae* strains, with inactivated pmt1 and pmt2 genes, respectively (paragraph 57 at p. 4); and teaches "These data show that heterologous proteins expressed in yeast are inappropriately modified by O-linked glycosylation. In turn, the modification can have

negative consequences on the maturation and activity of the protein. The inventors have established that coupling expression using an endogenous signal sequence with specific mutant strains deficient in O-linked glycosylation, the activity of heterologous proteins expressed in yeast can be drastically improved. Since there are 6 PMT genes in yeast that are non-redundant and exhibit differences in substrate specificity, deletion strains of any of the six genes may provide the needed inhibition of aberrant O-glycosylation. In addition, mutations can be combined to further promote proper folding. Thus the inventors have developed a novel solution for overcoming a problem that has limited the potential of low cost expression of commercially important molecules in yeast" (paragraph 71 at p. 6).

Gentzsch teaches pmt1 and pmt2 deletion mutants of *S. cerevisiae* (p. 28, column 2, paragraph 2.1); teaches the polypeptides encoded by pmt1 and pmt2 function as a heterodimer having O-mannosyltransferase activity in the O-glycosylation of polypeptides (p. 128, abstract); and teaches that disruption of each of these genes leads to "a dramatic decrease of mannosyltransferase activity in vitro" (p. 128, abstract).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of the '211 application to use a pmt1- and/or a pmt2-deficient strain of *S. cerevisiae*. One would have been motivated to do this because of the advantages of using such a strain as noted by Ng above.

Furthermore, claims 1, 6-9, and 12-18 cannot be considered patentably distinct over the claims of the '211 application when there is a specifically disclosed embodiment in the '211 application that supports the claims of that application and falls

within the scope of claims 1, 6-9, and 12-18 herein because it would have been obvious to one having ordinary skill in the art to modify the method of the claims of the '211 application by selecting a specifically disclosed embodiment that supports the claims, i.e., type III HPLC-12 as the recombinant polypeptide as disclosed at p. 11, lines 23-31 and p. 16, lines 7-8. One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within the claims of the '211 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

[15] Status of the claims:

- Claims 1, 6-9, and 12-18 are pending.
- Claims 1, 6-9, and 12-18 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656